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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/454,651	12/06/99	LINSLEY	P 30436.30USD1

023914 HM22/0913
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PATENT DEPARTMENT
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PRINCETON NJ 08543-4000

EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1644	14

DATE MAILED: 09/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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09/454651

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.

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MARY J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 6/14/01

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 11-19, 38-42 is/are pending in the application.
Of the above, claim(s) 13-19, 41, 42 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 11, 12, 38-40 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892 ☑ NOTICE TO COMPLY WITH SEQUENCE RULES
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Upon a review of the instant application, it appears that the each disclosed sequence does not have its own SEQ ID NO.

Therefore, this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825 (see the specification at page 10, line 20). However, this application fails to comply with the requirements set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

For example, see page 36, lines 22; page 62, lines 19-20; and page 77, lines 11-22.

Alternatively, applicant is invited to indicate which SEQ ID NO: on the Sequence Listing is relied upon for each disclosed sequence.

Applicant is reminded to amend the specification to indicate the appropriate SEQ ID NOS:.

Applicant is reminded to review the application for the sequence compliance with every disclosed sequence.

Applicant is required to fulfill these requirements.

2. Claims 11-19 and 38-42 are pending.
Claims 1-10 and 20-37 have been canceled previously.

3. Applicant's election with traverse of Group I and the species neoplasia in Paper No. 12 is acknowledged.
The traversal is on the ground(s) that the claims the groups of inventions are not independent and distinct, and (2) the examination of the entire application would not constitute a burden to search.

This is not found persuasive because the inventions are distinct as noted in the previous Restriction Requirement, as shown by the distinctness described therein. Applicant is reminded that MPEP 803 states that the Inventions be either independent or distinct and a burden on the Examiner if restriction is required. Also, applicant's attention is directed to MPEP 806.05 for issues of distinctness.
Regarding applicant's comments about undue burden, the MPEP 803 states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search".

In contrast to applicant's reliance on the generic ability of CTLA4 ligand to interfere with the interactions of CTLA4- positive cells and B7-positive cells; applicant is reminded that B7/B7 fusion proteins, CTLA-4 fusion protein hybrids, CD28/CTLA-4 fusion proteins , B7-specific antibodies, and CTLA-4-specific antibodies do differ in physiochemical structures of differ and modes of action to such an extent and require non-coextensive searches to such an extent that they are considered separately patentable. Antibodies, fusion proteins and hybrid fusion proteins do differ in structure and functional attributes.

In contrast to applicant's reliance on classification alone, the searches and issues between the Groups are not coextensive.

The Restriction Requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the examiner by the examination Groups. The Inventions are distinct for reasons elaborated in the previous Office Action.

Claims 11, 12 and 38-40 as they read on regulating CTLA4 T cell interactions and treating neoplasia with soluble B7/B7 fusion proteins are under consideration in the instant application.

Applicant is invited to provide a claim in independent form that is drawn to the elected invention.

While the species election of neoplasia is under consideration; it is noted that Group I comprises regulating different immune systems even though such regulation comprises both stimulation and inhibition of certain diseases and condition. his was done in the interest of compact prosecution. Inhibiting an immune response or disorder and stimulating the immune response differ to such an extent that they are considered patentably distinct.

4. In view of applicant's Petition to Correct Inventorship Under 37 CFR 1.48(b)(c), filed 6/18/00; the inventorship in this nonprovisional application has been changed by the deletion of Philip Wallace and Nitin Damle and by the addition of Robert Peach and Jurgen Bajorath have been added

The current inventors include Linsley, Ledbetter, Bajorath, Peach and Brady.

Applicant is requested to verify the inventorship of the instant application, given that the inventorship of the priority documents appear to differ from the inventorship currently indicated.

5. Applicant is invited to verify that the instant claims have written support and enablement under 35 USC 112, first paragraph, for the instant claims to USSNs 08/008,898, filed ½/93 and 07/723,617, filed 7/27/91 for methods of treating neoplasia with B7 and B7 fusion proteins as well as for B7-1 and B7-2.

6. It is noted that two Information Disclosure Statements (Paper No. 6, filed 8/3/00 and Paper No. 10, filed ½/01) have been submitted. However these are duplicates of one another

7. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant should amend the first line of the specification to update the status of the priority documents.

8. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

9. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).

10. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

11. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

12. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 11, 12 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A) Claims 11, 12 and 38-40:
Inconsistency in Treating the Elected Invention Neoplasia by Inhibiting T cell responses with B7.

With respect to the elected invention, claims 11, 12 and 38-40 are not enabled for achieving the elected endpoint of treating neoplasia by "regulating CTLA4-positive T cell interactions with other cells comprising inhibiting the interaction of CTLA4-positive T cells with B7 positive cells by contacting said T cells with a ligand for CTLA4 (i.e. B7 fusion protein)" or "regulating functional CTLA4 T cell interactions .... to interfere ... " because B7 fusion protein acts as an adjuvant by enhancing the T cell responses and not by inhibiting T cells responses, as currently recited.

Given the adjuvant activities of B7; the skilled artisan would have determined that B7 or B7 fusion proteins would be effective in treating neoplasia by inhibiting T cell responses.

For example, see Sturmhoefel et al. Cancer Research 59: 4964-4972 (1999).

In addition, see Figure 9 of the instant application.

Applicant should amend the claims to read on the elected invention, including amending the claims from any inconsistencies.

B) Claims 11, 12 and 38-40
Scope of In Vivo Treatment by inhibiting T cell responses with B7.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulatory-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting cognate T:B interaction s with certain antagonists of CD28:B7 interactions would be effective in regulating T cell interactions by inhibiting said T cells, particularly in vivo or in therapeutic methods to regulate cellular interactions and immune responses (see Summary of the Invention, particularly page 9, paragraph 1).

For example, page 50, paragraph 1 and Figure 9 of the instant specification indicates that B7 did not significantly inhibit the MLR even at higher concentrations.

There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed methods to inhibit functional CTLA4:T cell interactions to regulate cellular interactions and immune responses in vivo by administering B7 or B7 fusion proteins, commensurate in scope with the therapeutic methods encompassed by the claimed invention.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol., 1992; see entire document, particularly page 558, column 2).

Blazar et al. (J. Immunol. 167: 3250-3259, 1996) discloses that issues such as tissue distribution, half-life, affinity and avidity obtained with these various CD28-B7-specific reagents might prove to be highly important in achieving GVHD protection. However, any conclusion regarding the efficacy of CD28/B7 blockade on altering in vivo immune response should be interpreted in light of the type of reagent infused (Blazar see page 3257, column 2, paragraph 10.

Blazar et al. (J. Immunol. 167: 3250-3259, 1996) discloses that anti-CD80 or anti-CD86 antibodies were ineffective in preventing T cell CD8-mediated GVHD lethality; that each antibodies was partially effective in CD4-mediated GVHD lethality and that the combination of anti-CD80 and anti-CD86 antibodies were effective in preventing GVHD lethality in murine experimental models (see entire document, including the Abstract)

Similarly, Perrin et al. (J. Neuroimmunol 65: 31-39, 1996) discloses that in contrast to the effective treatment of disease with CTLA-4 Ig; anti-CD80 (B7-1) attenuated the first clinical disease episode but not the relapse, anti-CD86 (B7-2) had no significant effect on the course of disease, and the combined treatment with anti-CD80 plus anti-CD86 resulted in the exacerbation of disease (see entire document). It is also noted that CTLA-4 Ig had a marked but incomplete therapeutic effect in the EAE model.

In addition, Yi-qun et al. (Intl. Immunol. 8: 37-54, 1996) discloses that their findings have a number of important implications for therapeutic approaches (see entire document, particularly Discussion, last paragraph). It is clear that inhibition of T cell response to soluble antigens will require the blocking of both B7-2 and B7-1 to be effective. More, important it is unlikely that ongoing T cell response will be susceptible to inhibition by anti-B7 reagents, for example in autoimmune diseases.

Therefore, it is acknowledged that the administration of the CD28:B7 inhibitor CTLA-4 Ig can result in immunosuppression as observed in several model systems. However even in these systems; the timing of CTLA-4 Ig administration relative to the antigenic exposure of the mechanism by which the foreign antigens were introduced into the host (e.g. timing, dose and site) had significant impact on the success of the intervention.

In contrast to the role and avidity that the CD28:B7 inhibitor CTLA-4 Ig appears to have in vivo, there is insufficient objective evidence in the instant application that either the claimed B7 or B7 fusion proteins alone can inhibit T cell function or interactions in vivo and the objective evidence above would indicate that neither would be predicted to inhibit in vivo function or interactions.

Immunosuppression and inhibition of leukocyte interactions and functions are much easier to achieve under controlled in vitro conditions that experienced in the human immunoregulatory diseases targeted by the claimed invention. Further, in animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Therefore, it should be noted that although the animal models validate concepts based on studies of human disease, such studies are limited to the acute as opposed to chronic nature of the disease. Immunosuppression is much easier to achieve under such controlled conditions to defined antigens in mice than that experienced in the human immunoregulatory diseases targeted or encompassed by the claimed invention.

The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by B7 fusion proteins. The specification does not teach how to extrapolate data obtained from the disclosed in vitro assays based upon the claimed B7 Ig or from other CD28:B7 inhibitors such as antibodies (e.g. anti-B7 antibodies) or CTLA-4 Ig to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention. Therefore, there is insufficient objective evidence that accurately reflects the relative efficacy of the claimed method or therapeutic strategies to inhibit T cell proliferation or to prevent binding of CD28 receptor to B7 antigen, commensurate in scope and encompassed by the claimed methods.

Furthermore, the disclosed uses encompassed by the claimed methods are the inhibition of autoimmunity, transplant rejection, and infectious disease (see page 32, paragraph 2 of the instant specification). Based upon the objective evidence disclosed in the instant specification and in the art, the skilled artisan could not predict the efficacy or enablement of B7 or B7 fusion proteins to inhibit CTLA4:T cell interactions by inhibiting T cell functions in the targeted diseases or patients encompassed by the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting T cell function and interactions.

14. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 11, 12 and 38-40 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing a "ligand for CTLA4" and "B7" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics are not set forth in the specification as filed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Page 9, paragraph 1 discloses CTLA4-specific antibodies and B7Ig fusion proteins as CTLA4 ligands. Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any CTLA4 ligand that results in the desired inhibitory effect, yet the instant specification does not provide sufficient written description as to the structural features of said CTLA4 ligands and the correlation between the chemical structure and the desired binding and inhibitory function. The reliance on the disclosed limited examples of CTLA4-specific antibodies and B7Ig does not support the written description of any CTLA4 ligand. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different pharmacological activities. Therefore, structurally unrelated CTLA4 ligands encompassed by the claimed invention other than CTLA4-specific antibodies and B7Ig would be expected to have greater differences in their activities. It is noted that CTLA4-specific antibodies and B7Ig do not share critical common structural attributes, as antibodies and fusion proteins differ in structure and physicochemical properties. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

Page 5 of the specification discloses two members of the B7 family, namely B7-1 an B7-2 and pages 34-39 of the specification discloses the construction of B7 fusion proteins, which appears to be only B7-1.

Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any B7 molecule that results in the desired inhibitory effect (or stimulatory effect as it reads on treating neoplasia), yet the instant specification does not provide sufficient written description as to the structural features of said B7 molecules and the correlation between the chemical structure and the desired binding and inhibitory (or stimulatory) function. The reliance on the disclosed limited examples of B7-1 and B7-2 does not support the written description of any B7. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

The instant claims do not provide functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variable, CTLA4 ligand alone or B7 alone is insufficient to describe the genus of inhibitors (or stimulators) to be employed in the claimed methods.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of CTLA4 ligands or B7 molecules or fusion proteins, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

15. Claims 11, 12 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "B7-1 and B7-2" (and the non-elected CTLA4-specific antibody) as the claimed CTLA4-ligand and B7 protein or B7 fusion protein, does not reasonably provide enablement for any "CTLA4 ligand" or "B7 protein or B7 fusion protein". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies CTLA4 ligands or B7 proteins / fusion proteins other than those encompassed by B7-1 and B7-2 as disclosed in the specification as filed. CTLA4 ligand and B7 may have some notion of the activity of the polypeptide in costimulation of T cells, claiming biochemical molecules by a particular name given to the protein (i.e. CTLA4 ligand or B7 by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any CTLA4 ligand or B7 protein / fusion protein..

Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in comstimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any B7 molecule that results in the desired inhibitory effect (or stimulatory effect as it reads on treating neoplasia), yet the instant specification does not provide sufficient guidance and direction as to the structural features of said B7 molecules and the correlation between the chemical structure and the desired binding and inhibitory (or stimulatory) function. The reliance on the disclosed limited examples of B7-1 and B7-2 does not support the enablement for any B7 protein or fusion protein.

In addition, page 9, paragraph 1 discloses CTLA4-specific antibodies and B7Ig fusion proteins as CTLA4 ligands. Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different pharmacological activities. Therefore, structurally unrelated CTLA4 ligands encompassed by the claimed invention other than CTLA4-specific antibodies and B7Ig would be expected to have greater differences in their activities. It is noted that CTLA4-specific antibodies and B7Ig do not share critical common structural attributes, as antibodies and fusion proteins differ in structure and physicochemical properties.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. CTLA4 ligand) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects CTLA4 ligands and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. . Because of the lack of sufficient guidance and predictability in determining which structures would lead to CTLA4 ligands and B7 proteins with the desired claimed properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of CTLA4 ligand and B7 proteins and fusion proteins.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus, applicant's reliance upon CTLA4 being the specificity of CTLA4 ligand or that B7 connotes a family of costimulatory molecules without further structural functional analysis does not appear to provide sufficient enabling support for any CTLA4 ligand or B7 protein or fusion protein and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Without sufficient guidance, making and using CTLA4 ligands and B7 proteins and fusion proteins would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

16. Claims 11, 12 and 38-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) With respect to the elected invention, claims 11, 12 and 38-40 are indefinite in its recitation of "regulating CTLA4-positive T cell interactions with other cells comprising inhibiting the interaction of CTLA4-positive T cells with B7 positive cells by contacting said T cells with a ligand for CTLA4 (i.e. B7 fusion protein)" or "regulating functional CTLA4 T cell interactions .... to interfere ... " because B7 fusion protein acts as an adjuvant by enhancing the T cell responses and not by inhibiting T cells responses, as it reads on treating neoplasia as the elected invention.

For example, see Sturmhoefel et al. Cancer Research 59: 4964-4972 (1999).

In addition, see page 50 and Figure 9 of the instant application.

In addition, the recitation "regulating" is indefinite because it is ambiguous as to the nature, direction (positive or negative) or degree of said modulating. Therefore, the metes and bounds of the claimed methods and functions and/or endpoints are not readily apparent or inconsistent with the intended consequences.

B) Claims 11, 12 and 38-40 are indefinite in the recitation of "B7" in that they only describe the products of interest by an arbitrary protein name. While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein and fusion proteins thereof. Applicant should particularly point out and distinctly claim the "B7 protein" and "fusion proteins" thereof by claiming sufficient characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of.

In particular, applicant is invited to clarify the metes and bounds of B7 with respect to priority. It does not appear that B7 as it reads on B7-1 and B7-2, as disclosed on page 5, paragraph 2 of the instant specification has written support in priority documents USSNs 07/723,617 and 08,008,898.

C) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

18. Given applicant's elected invention; the prior art is applicable as it reads on treating neoplasia with B7 and B7 fusion proteins for examination purposes under art.

However as noted above, this therapeutic endpoint appears inconsistent with the claimed recitation of "interfering" and "inhibiting" T cell responses.

Again, applicant is invited to amend the claims to clearly read on the elected invention and species.

19. Claims 11-12 and 38-40 are rejected under 35 U.S.C. § 102(e) as being anticipated by Linsley et al. (U.S. Patent No. 5,580,756).

Linsley et al. teach the use of B7 and B7 fusion proteins to inhibit neoplasia (see entire document, including Summary of the Invention, Detailed Description of the Invention such as columns 5-11 and Uses In Vitro and In Vivo, particularly columns 12-13).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced B7 molecules to treat neoplasia and cancer.

It is noted that U.S. Patent No. 5,580,756 has priority back USSN 07/498949, filed March 26, 1990.

20. No claim allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

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September 10, 2001